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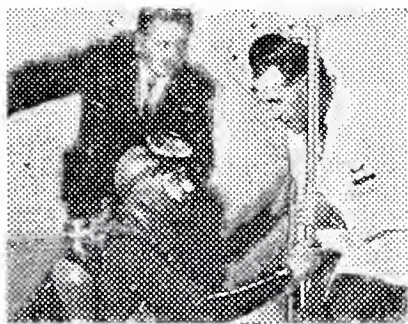
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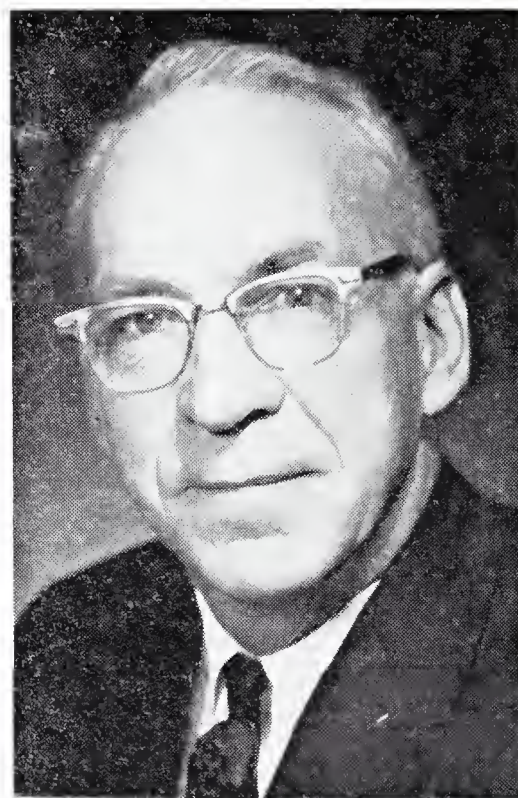
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Guest Editorial

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It is an honour to be invited to be a guest Editor for this issue of our own Medical Journal. Many distinguished physicians, both graduate and undergraduate, have contributed articles for this Journal in its long history, and it is a serious responsibility to attempt to discuss briefly some of today's problems which are relevant and immediate.

Recently, after discussing a medical case with some undergraduate students and residents, a question was asked, "What are the major problems which worry students today"? The answer was that students are very worried about socialized Medicine and Government control in their choice of graduate training and type of practice — as a general practitioner, specialist, solo practitioner, or in a group. It is a serious mistake for the Government or the University to try to direct students into one specialty or another, or into general practice. Nothing will cause deterioration of medical care as rapidly as having dissatisfied doctors practising in a way which is neither congenial nor for which they have no aptitude. Furthermore, it is still too early to know what the pattern of practice will be in the next generation. Even if the powers-that-be could so direct our lives, selection for general practice, country practice, and research scientists would have to be considered at the time of accepting students into Medicine, rather than at the completion of their training. Many, if not most physicians, change their direction once or twice after starting their training. Some well trained researchers become University presidents. It does not seem to me wise nor practical to be concerned about the present flurry over too many of this specialty or not enough of that. Take training in the area which has the greatest interest for you and not what will provide a sure job. Certainly we know we do not have enough practising physicians. You may wish to do family practice, or General Medicine, or General Surgery and have a special interest, a hobby, as well. It is hoped that you will return for a brush-up or further training every five or ten years. If this becomes the normal practise then teaching hospitals must provide opportunities for this kind of graduate training.

Regardless of statistics, there are not enough doctors for the provision of the best medical care today. When patients are unable to get appointments for weeks and sometimes months, with the doctor of their choice, they forget there are not enough doctors and become critical. Most doctors are working hard, too hard, and are sensitive about criticism. This increased work load is due in part to the fact that more sick people are kept alive. There are more older people and they have greater needs for medical service and many more diseases can be treated today. Treatment is often sophisticated and expensive, which cause a great increase in the cost of medical care. Doctors are usually blamed for this. The need for medical insurance is recognized throughout the Western world, and the need for incentives such as the fee for service is also recognized. Most people also realize that operations directly under Departments of Government tend to be less efficient than those which are even partly separated by being under a commission or a

Crown Company. The danger of becoming Government servants is not very great if we provide first class service, if we are available and if we provide coverage for under-doctored areas. However, the medical profession must learn how to deal with Government. We must provide leadership and not always fight a rear guard action. We really have nothing to fear as long as we do not lose the role which history has asked us to accept. The crisis in medical care is not the large incomes that a few unscrupulous doctors may be making, as publicized on the front page of some of our local papers, but rather the failure of the profession to maintain its honoured role, and to accept its responsibility for quality and adequacy of medical care. We have become so frightened of socialized medicine that we have forgotten the power of integrity. We can deal with Government if we have the people, our patients, behind us.

We are worried because patients have lost their blind faith in their family doctor. In the old days it was, "Drunk or sober, my doctor is still my doctor". Now it is, "I haven't a family doctor and can't find one". This change in attitude is not just because patients are more knowledgeable and more critical, but because doctors today prefer to practice with logic rather than with authority. Patients are encouraged to follow a doctor's suggestions because they make common sense, not because they are said by a superior being. Sometimes there is no suggestion, there is no common sense. Previously, many diseases could not be treated, and the doctor wasn't worried. Now if there is no treatment a doctor feels insecure. He must be scientific. Yet science has let him down. Science has let us down in that it changed our ideal. Originally, the ideal of the profession was to be of service. Later it was to be scientific — find the cure for the disease and let the patient get better. The cold scientist was rated above the sympathetic humanist. However, the members in the profession whom we admire most are individuals who have a proper balance of both sets of characteristics. Now our ideal is not clear, but doctors are placed in a preferred position. It is because so much is demanded of the profession that its role has been placed above that of others. We are no better as physicians than others in society, but more is expected of us. It may be because we are shy, embarrassed and hesitant about accepting this role that we are insecure and afraid of the future.

The profession has been criticized for its lack of responsibility for professional excellence and integrity. However, the College of Physicians and Surgeons of Ontario previously did not have the support of the law to do this properly, and certainly did not publicize what was being done in this regard. "Let not your good be evil spoken of" is good advice. The College is now involving more non-medical members of the society who can appreciate the difficulties and give support for what the profession is trying to do. It has been suggested that students take little responsibility for the professional excellence of their class or of their clinics. Medical students are the "cream of the crop", hard working and serious, it is harder to get into Medicine than any other Faculty. Do we recognize that more is expected of us, that patients trust us, and respect us. Seldom does a clinic bring pressure on a member who is delinquent in attendance, disinterested in his performance, or unprofessional in his attitudes. Students who have failed or have withdrawn seldom recount any specific help from classmates. When day to day assessment is the ultimate criterion of "pass or fail" it is most important that students take responsibility for each other's training.

The profession, both graduate and undergraduate, have failed to accept responsibility for the needs of society because we are so busy serving the needs of the individuals. The only serious criticism made against the profession in its lack of availability. Our profession should delineate the areas where more doctors are needed and provide incentives to develop more effective way of providing medical coverage. When we graduate we must be willing to give some time serving these communities either in Canada or abroad. The profession must be ahead of the Government in recognizing deficiencies in our provision of medical care, rather than complaining when criticisms are made.

Possibly medical students rush into the science of Medicine without a good grounding in the humanities and social sciences. We would agree with Hippocrates, "The life is so short — the craft so long to learn". More and more of what doctors did previously as a matter of course, possibly in a hurry rather than in the most satisfactory way, is being turned over to sociologists and paramedical professions. This may be necessary because of the lack of time and the rather complicated structure society uses in providing certain services, but if this is to be done well the doctor also must have an understanding of the non-medical problems his patients are facing. This means greater knowledge and continued interest in social sciences.

There will always be too much work to do. Sir William Osler said WORK was the master word in Medicine. Doctors and medical students do have a heavy work load, but probably DISCIPLINE is a more important word for us all. Discipline to organize our reading time, discipline to organize our spare time so that we can make the most of our recreation — sport, music, books. We cannot expect to catch up on these cultural supports for heavy work loads after we finish our specialty, or after we get settled in prac-

tice. The discipline of living must start as we start Medicine and become more strict as each year goes by.

We cannot be good physicians if we are not healthy with the joie de vivre to share with our patients. We cannot help patients meet their tragedies without spiritual values which need daily nourishing. Remember Joseph Addison's observation, "Tis not in mortals to command respect, but we'll do more . . . we'll deserve it". Let us remember the high role that society has given us. Let our commitment give us confidence and our humility make us friends. William Cooper said, "Knowledge is proud that he has learned so much. Wisdom is humble that he knows no more".

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Medical History Writing

W. T. W. Clarke, M.D.*

Every textbook on medical diagnosis contains a chapter on history-taking, yet no one has ever learned to take histories by reading. This article is intended to inspire a philosophy of history-taking and to suggest practical points in achieving the desired end. You will forgive me if it is moulded particularly for final year students working on the medical wards of the hospital under the present teaching system. However, this is a vital part of the course and the principles are much more widely applicable. Many of the lessons learned on the wards will be practised by the doctor for the remainder of his life.

We are all aware that a good history is the most important factor in the majority of diagnoses. Most diseases can be identified by careful analysis of the symptoms before there are any diagnostic findings.

Though we do a "complete" physical examination on every patient, how we look and what we find are greatly influenced by what the history suggests. One example of this is in examination of the spleen. The routine is to place your hand at two or three different places in the left upper quadrant and ask the patient to take a deep breath. However, if the history of a certain patient has suggested a possible diagnosis of infectious mononucleosis, you will place your hand on four or five different places. You may spend some minutes teaching your patient that difficult feat of making the diaphragm descend when she breathes in instead of the usual paradoxical response when she is asked to breathe deeply. Then you go on to other tricks: stand at her left side and hook your fingers over the costal margin; roll the patient on her right side, and so on. Such detail is not practical for your routine examination of every portion of the body. Others often add important physical findings because the history is more significant to them and leads them to look particularly regarding those findings.

From what has already been said it is obvious that the history not only leads to the diagnosis but also reveals the history-taker's differential diagnosis and thought processes in working out the problem, his knowledge of diseases and even his curiosity about the uncounted, as yet unanswered, problems of sick people. Arriving at a correct diagnosis is the least important gain of the student history-taker. Indeed, I have often been pleased in examining students' histories to find a wrong diagnosis at the end when it means the student has attempted to see the problem and work it out for himself. He has certainly learned more from that experience, and also from his mistakes, than he could ever gain from the chart or the internes.

The inter-personal encounter of taking a good history is one of the best examples of the art of medicine. You

have to gain and keep rapport, confidence that you are wholly interested in helping your patient, and his active, eager co-operation in working with you. You have to bring him into a world of precise definition that is entirely foreign to him. You have to obtain his best possible recall of observations that meant nothing to him. You have to get fine distinctions made without asking leading questions. The patient must think he is pleasing you without getting notions that any particular answer pleases you more than an alternative or a negation. If you antagonize him, all is lost. And all this with a patient who is sick! Surely the lawyer's cross-questioning of a witness whose feelings mean nothing to him is simple in comparison. Perhaps because of youth and certain personality traits, I occasionally find myself taking a history from a patient whose manner, probably aggravated by his illness, gives me an urge to poke him in the nose. You take histories from all sorts of people, people more clever than yourself and stupid people, garrulous and taciturn people, complainers and stoics. To do this you must acquire an understanding of the nature of the person as you are taking his history. And, as if all this did not make the task sufficiently difficult, it must be adroitly pursued while you are thinking of the differential diagnoses, recalling distinguishing points and making difficult judgments.

The final point in the importance of the history-taking is that it is always part of the therapy, sometimes the major part. It is the first impression you make. It is how you deal with this patient. What could be more important to him?

All this emphasizes not only the great value of the history, but also that constant thoughtful practice is the only way to learn how to do it. Your technique and skill should continue to improve for the rest of your life. Every opportunity to take a history should be a step up the endless ladder of the art, perhaps comparable to another rally in the lifetime of the professional tennis player. Seize upon it eagerly, realizing its tremendous value. This is not schoolboy stuff, not intellectual drama. This is real life as only the doctor is privileged to live it.

The plan of your history-taking may be changed to suit your needs and experience. There is a very valuable outline widely used in Toronto's medical school, printed by the University of Toronto Press, and commonly called "the green book". The main headings in this are so standard that I believe a great deal of time can be saved by omitting or abbreviating them. This is a matter of personal taste, but surely the record should be concentrated on the most valuable information. For example:

Thomas Jones, 48

contains as much information as

Name—Thomas Jones

Sex—Male Age—48

*Fellow in Medicine and Therapeutics.

This article has been reprinted from Volume 28 of this Journal in the aim of providing students in Period II A with an introduction to this most necessary of bed-side skills. Professor Clarke is currently in the Department of Medicine, University of Toronto.

Headings such as Chief Complaint and History of Present Illness can be abbreviated to C.C. and H.P.I., or even omitted: but, no matter how headed, these subjects must be taken up in distinctly set apart divisions. I try to use words accurately and to avoid ambiguity, but do not necessarily attempt to construct sentences for everything. There is no need for repetition: if you enquire into weight change in the history of present illness, do not record it under General and Gastrointestinal also. You haven't time; the observant reader will find it, and will pay more attention to it if your history is brief.

Under GENERAL INFORMATION the date of taking the history is vital: in reviewing files it is one of the most aggravating omissions commonly encountered. There seems to be little point in listing marital status, occupation and race here, as these are almost invariably dealt with at greater length in Personal History.

The CHIEF COMPLAINT must be brief, a few words, possibly the patient's own, and a time factor.

The HISTORY OF PRESENT ILLNESS is the chief work of your history. It should contain every relevant point about the disease and how it affects this patient. You should read up the disease and return to ask more questions that will occur to you with study and thought. I do not attempt to stick to a chronological order for everything, but rather try to organize the facts into a diagnosis. For example: if it appears to be a disorder of cardiovascular function, every question regarding this system should be asked and the answer noted here. There should be no heading Heart in the functional enquiry for that patient. If the present illness appears to involve more than one system, the history is usually more meaningful if each system is placed in a separate paragraph and fully dealt with there. If there are some isolated symptoms that do not appear to fit or are not understood, they must be noted, but this can be done at the end of Present Illness. If the history is obtained from a patient who is unable to co-operate, note the difficulties. If a history is obtained from different sources, place this information in a separate paragraph and clearly indicate the source. Although you describe the entire illness from its onset, you must enquire into exactly what brought the patient to the doctor or the hospital at that particular time. The history of present illness is where the finesse of getting facts is needed. For example: When the patient says "a long time", you know this is meaningless yet cannot tell him that in so many words. If you say "ten seconds or ten years?" he may feel insulted, and you have lost the play. If you say "two or three years?" he may say "yes" to please you or to save himself the trouble of recalling. It may be necessary to say, "I realize you can't immediately recall the exact details but it would help to know if it would be a matter of months or years", (adjusting the example to what would be reasonable for the complaint, such as seconds or minutes for

recurring abdominal pain). He replies "years" or "a few months", and you counter with "three or four?" or "eight or nine?" The extent to which you push this sort of enquiry will depend on many factors, such as how much practical help the exact time gives you, how sick the patient is, how accurately he appears to be able to recall. Whether the patient can or cannot exactly place the onset of a symptom tells you much about that symptom: it suggests how suddenly it started, how severe it was, and how much it meant to the patient. Your attention and interest in his answers will draw forth greater efforts on his part. In approaching patients you will find many who are too ill to give detailed histories and some who just do not want to bother. There is no way of altering the fact that the patient is ill and that you may be "just the student" and second (or fourth) enquirer, and not *the* doctor really responsible for him. Of course you adjust your demands to the situation. If the patient is orthopnoeic and cyanosed you feel his pulse and ask him to put out his tongue — you are really observing him closely. You quickly look at his neck veins, feel for the apex beat, percuss his axillae and outline his heart, listen over the front and sides of the chest, feel for his liver and press the important sites of oedema collection; all this can be done without disturbing him. When the patient sees that you are considerate and know what you are doing, it is surprising how much information he will give to help you. Ask what you feel justified in asking at that particular time. You have learned what can only be learned by handling the patient when acutely ill and have established good rapport for your return that afternoon or the next day. The ease and skill with which you take the history means not only that you ask better questions, but that you receive better answers from the patient. You have his confidence and you are enabled to help him more by making a better diagnosis. Though this must be acquired by practice, you can have such questions as: What kind of pain? Where? How big? How deep? Continuous or intermittent? Aggravated by? Eased by? Any associated symptoms? etc., learned by rote and at your tongue-tip. These aspects are enquired into innumerable times. They must become almost automatic so that you ask them with no effort.

It is much more difficult to remember all the manifestations of a disease or of disorder of a system while actually taking the history from a patient than it is to recall the same details to answer an examination question. Your knowledge of the symptoms of diseases should be so thorough that you enquire into these details almost subconsciously. It is a way of thinking that comes only with experience. This is why your work on the wards — on your own — is the most important part of your undergraduate course. Your teachers can suggest and criticize, but you must do the job. Great indeed is the University that can accomplish this step in learning, and a University is only as great as its students.

All of us have been beginners and we realize that, for many, there is almost a mental block when, alone, they confront their first real live patients. This quickly disappears with practice and the acquisition of skill. The interest of medicine becomes tenfold as one changes from a thinker to a doer, from pathology to patients; it is the greatest but the most difficult step because *you* must take it by yourself.

The FUNCTIONAL ENQUIRY must be brief. It should not contain a great many negative or normal observations; recording all the questions in the "green book" is to be abhorred. Some judgment is required to know the common symptoms of disordered function of each system; if these are absent, the details can be omitted. Furthermore, these can be recorded in the briefest fashion possible. An example for the case where there is no cardiovascular or respiratory disorder: "Chest—no cough, hemoptysis, pain or other distress. C. V.—no dyspnoea or oedema". A positive statement of exercise tolerance such as "hurries up 2 flights of stairs readily" is even better than "no dyspnoea". When enquiring about chest pain you should also ask about pleurisy, pain from the heart, palpitations, and other forms of distress in the chest. These specific questions and associations asked in the layman's language, sometimes remind him of symptoms that he might otherwise omit. A brief recording of the data in technical terms as exemplified above gives time to ask the questions. More detail is asked than recorded. However, judgment is still required to avoid asking unnecessary details in the systems that appear normal. Some sections in the "green book" are intended more as a guide where there is disorder. Although there may be something to be said for writing out the fuller form of questioning in your histories as a way of learning it, I would suggest that it is easier to write than to do. Concentrate on doing.

When symptoms that are part of the present illness are found in functional enquiry, they should be placed in the History of Present Illness. Other unrelated illnesses are described carefully here, but there should be no repetition of the Previous Health section. Some people are ready complainers and here is a chance to learn this. It is often a help in assessing the complaints in the present illness. Furthermore, here are elicited symptoms of which anxious and nervous people commonly complain — dizziness, fatigue, sighing respirations, palpitation, indigestion, etc. Of course each of these should be analyzed carefully to establish its cause, and they must be noted because of the help they give in understanding the patient. He will tell them to an interested physician asking about his various organs readily than if he suspects enquiry is being made into psychiatric aspects.

The PREVIOUS HEALTH is the most abused section of the routine enquiry, often even headed wrongly. Yet I believe that next to the history of present illness it is the most valuable. Let us clearly understand its purpose.

If you are going to pay anything more than lip service to the psychosomatic concept, to the patient as well as to his disease, this is your golden opportunity; and you cannot be a good doctor without such consideration. Here is where you establish your understanding of the patient's share of vigor and how he responds to life's blows, thus helping to gain the best insight into what sort of person he is. You will learn much that an obviously psychiatric interview may fail to uncover. Begin by asking directly about previous illnesses, many having been dealt with already in the Functional Enquiry. However, a little association is a great reminder. The technique of this is to enquire into the personal history simultaneously. Much more will be learned about both, often much more than even the patient realizes. A chronological enquiry is best. First ask the patient if she has been told anything about her birth and infancy. Perhaps you will learn that she was a hypertonic baby, although that has not been a fashionable diagnosis for long. Does she recall ever being sick in bed in the pre-school years? ever been seen by a doctor? any enuresis, night terrors or fits of temper? Each era in the patient's life is gone into carefully regarding not only any sickness or trips to the doctor but also how she felt generally, as indicated by how active she was and what she accomplished or was limited in. All through life we are sizing up people, our relatives and friends, our associates at work and at play: this plays an important part in how we get along in the world, no matter what our work is. These assessments are often subconscious, made on the basis of many impressions such as appearance, dress, voice, interests, responsiveness, knowledge, intelligence, judgment, etc. Some are endowed with the knack and may become very expert; we all must practise and try to improve. Even with the insight of a Shakespeare, one can still know the patient better by enquiring into his past.

The second great value of this section is the opportunity to increase your medical experience. We are all young in the life of the art. Here is your chance par excellence to learn about the outcome of many illnesses which, otherwise, can only be gained by many years of observation. Many students' and internes' entire medical experience is gained in a large teaching hospital. The patients admitted are selected and usually have major illnesses and illnesses requiring difficult therapy. However, from their previous illnesses, one learns that a great deal can be learned about the symptoms, effects of treatment, and course of those disorders that will form the greater part of one's practice. It is important to enquire into the symptoms of these other illnesses in sufficient detail to satisfy yourself with their diagnoses.

The third feature of this section is the only one that is observed consistently and yet is certainly the least worthwhile. If you discover an illness that has significance regarding the Present Illness, you will deal with it there. If the present illness is, for example, one of the acute exanthemata, you will establish those the

patient has already had in the history of Present Illness. I can see little or no point in recording a list and dates of acute illnesses from which the patient has recovered completely, often accepting his word for the diagnosis or, worse still, what he thinks the doctor thought it was.

A good deal of the PERSONAL HISTORY has been taken with the history of previous health and may be recorded there, or here, whichever proves clearest and briefest.² One of the important points in good history-taking is versatility. You must be able to strip your record of apparently unrelated features to their barest essentials but, at the drop of a hint, you must go into the greatest detail so that its true significance may be learned and recorded. This is particularly important in the personal history. For example: it is always necessary, even in the case of a simple fracture, to note the setting in which the patient became ill, what sort of home he will return to, what responsibilities he has, who is paying his medical bills and what financial impact they may have. The patient's job and what he actually does there must be known. By this stage of the history the importance of the so-called functional aspects, the patient's personality and way of responding will be evident. This will determine in what detail it is necessary to get to know this patient. Can the complete history be taken at once, or will several interviews be necessary? Can it be taken on the ward, or will you have to see the patient privately the next time? Because a student takes only two or three histories each week, he has unlimited time, giving him a great advantage over the doctors. You may, through time and interest, get to know the patient better than anyone else. Make full use of such opportunities to acquire skill in this very important aspect. You will be amply repaid.

In the FAMILY HISTORY one wearies of reading:

Father—died of old age at 88

Mother—died at 63, cause unknown;

and, similarly, a long list of siblings. Often this is followed by denial of such diseases as hayfever, asthma, migraine, cancer, tuberculosis, etc. In most cases the information desired is that regarding the disease, or diseases, from which the patient suffers. Was he exposed to it by heredity, or by environment? in relatives or associates? This may have been noted in the History of Present Illness. If it has and the problem is simple and largely organic, the family history section can be omitted. It is often revealing to enquire about relatives that have died while still young; hereditary factors then seem more significant. The loss of a parent in childhood or a broken home is momentous. In other cases, if it is of considerable importance to know the patient's nature, it is important to know the nature of those who have most influenced him by their germ plasm or their presence. Were they crazy, or just queer? What was the patient's attitude toward them? Whom does he consider

that he takes after? Eliciting such information requires time and skill.

I would like to mention a few points that are applicable to the recording of the PHYSICAL EXAMINATION. One sometimes hears a slightly skeptical reference to "those long medical histories". It should now be obvious that the recorder shows poor judgment and inability to think precisely if irrelevant parts are long. One might enquire as to why the functional enquiry and routine physical examination are recorded at all. If your history form was perfected and standardized, you might omit all negative information. You would then conclude that everything in your particular routine that was not recorded was investigated and found negative or normal. However, your knowledge and interests are always changing. For us who are just beginning to learn the art, it is especially valuable to practise thoughtfully picking out the important features to record as concisely as possible. The better we learn to do this, the better we will be able to take histories for the remainder of our lives. Good histories will be a major factor in our success with patients. Further, we have a debt to the records we make. This is particularly true in a group or institution if the records are to be of value once the acute episode is ended. Where different people are working from year to year it is necessary to record more. One experienced physician who knows his routine, his interests, and that only he will be using the records may be able to omit many negative findings. It is surprising, however, to look back on your own histories of a few years ago and realize how much you have forgotten about those individual patients. Sometimes you feel that you really did not know anything at all about medicine at that time—this may give you the impression that you do know something now. But it is very satisfying and helpful when you find that you had then considered systems that only now have become involved, and had recorded their condition.

In spite of the philosophical argument to the contrary, I use the word normal. Everyone realizes that it must mean within the central part of the normal range. It is not necessary to describe the disc, arteries, veins, retina and macula in patients in whom there is no reason to suspect that they might be, or become, abnormal. Looking back at an early history of a patient who now has retinal degeneration, to find the statement "fundus normal" greatly increases the probability that they were examined and that there were no lesions at that time. On the other hand, to say, "Heart—rate normal, rhythm regular" is inefficient when you can record quantitative information in even less space: "Heart—80, regular" conveys the facts. Another example: "Chest—movement good, equal, percussion and auscultation normal", is adequate if history points to no disorder here. There is no value in recording a purely differential point such as tactile fremitus. It is surely worth testing objectively and recording the major function of important special

(Continued on page 100)

The Adult Respiratory Distress Syndrome

Ron Grossman

It has recently been shown that a variety of direct and indirect pulmonary insults can lead to a syndrome of marked respiratory distress, hypoxaemia refractory to O₂ therapy, diffuse pulmonary infiltrates on x-ray and hyaline membrane formation. Previous terms for this clinical picture have included capillary-leak syndrome, congestive atelectasis, post-pump lung and shock lung. Because of the similarity of the clinical and pathological findings to that of the Respiratory Distress Syndrome of the Newborn, the term, the Adult Respiratory Distress Syndrome (ARDS) has been formulated.

CLINICAL FEATURES

Within 24 to 48 hours of the onset of serious illness or trauma, patients may suddenly develop marked tachypnea, dyspnea and cyanosis that is refractory to O₂ therapy. Minute ventilation is strikingly elevated and respiratory rates above 30 are invariably present. Intercostal and suprasternal retractions are seen on inspiration. Auscultatory findings are usually scant in the early stages. Bronchial breath sounds are present later in the course of the illness and crepitations are usually not present.

Chest films closely follow the clinical course. A patchy, bilateral alveolar infiltrate will develop first, fol-

lowed by a more confluent pattern. Just before death the appearance is one of diffuse consolidation.

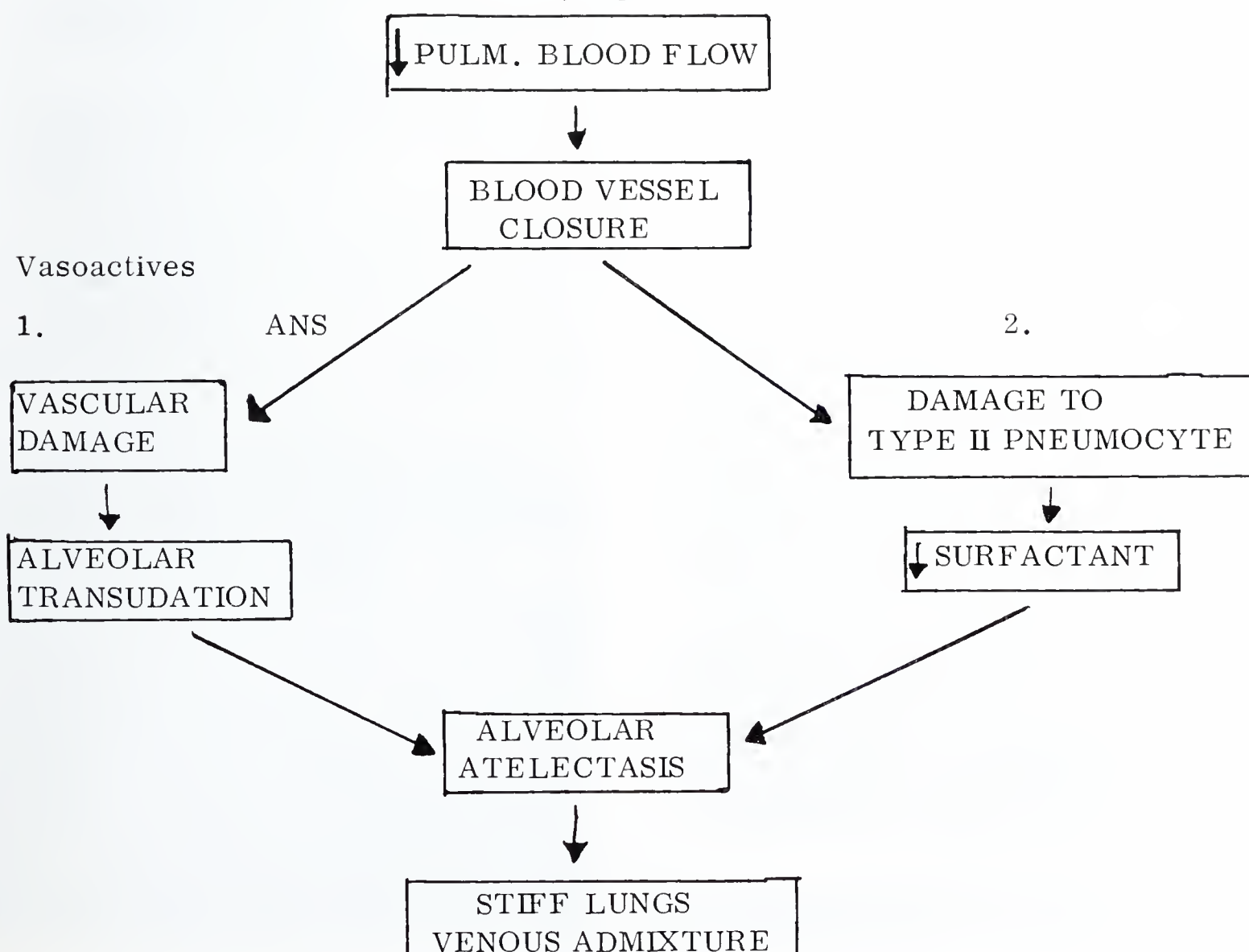
All patients will show a progressively decreasing static compliance and increasing pressure requirements when on a ventilator.

Hypoxaemia is the predominant feature and arterial blood gas determinations invariably show marked hypoxaemia despite high inspired oxygen tensions. Arterial blood pCO₂ is more variable — usually below normal values but terminally there is CO₂ retention. Hydrogen ion concentration tends to be normal in most patients with acidosis being present with severe hypoxia or or hypercarbia.

ETIOLOGY AND PATHOPHYSIOLOGY

1. Viral pneumonitis — Type 7A
2. Fat emboli⁴
3. Cardiopulmonary bypass
4. Shock¹⁴
5. Pancreatitis
6. Respirator lung⁶
7. Oxygen toxicity¹⁷
8. Heroin talc¹⁰
9. Massive transfusion

FIGURE 1

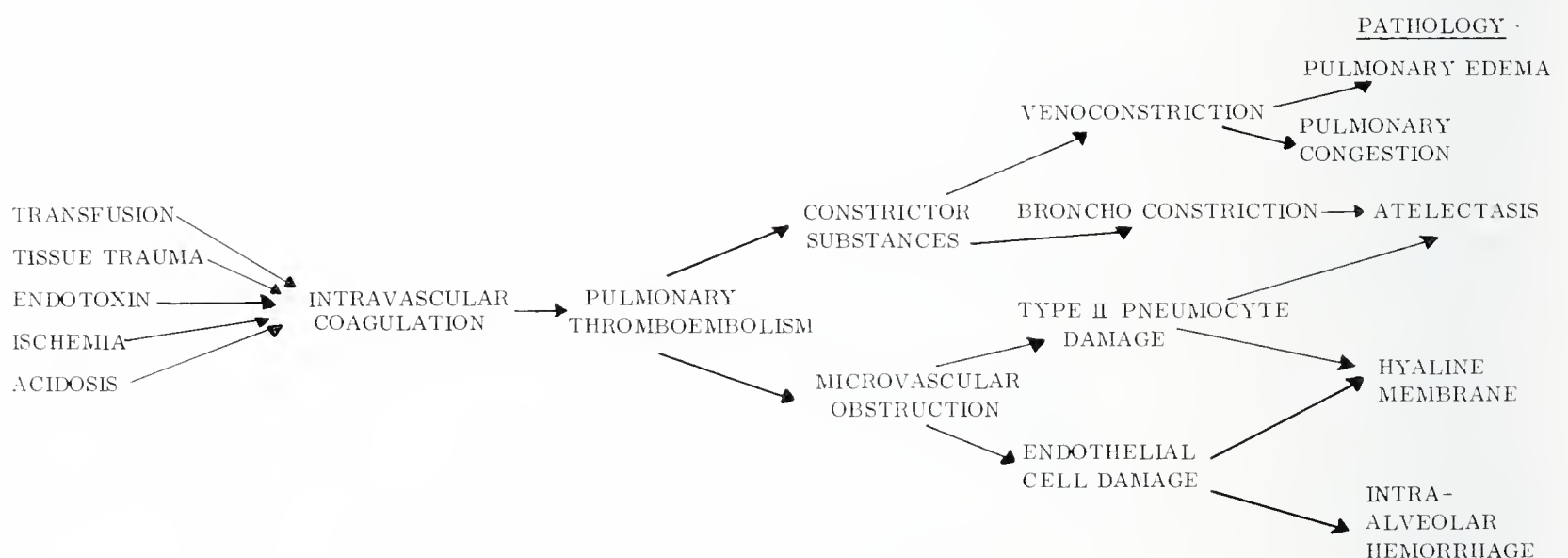


Fluid overload also seems to play a predisposing role. Theories of how these varied insults can lead to diffuse pulmonary injury have followed a number of routes. Berkofsky⁷ has suggested that a decreased pulmonary blood flow leads to blood vessel closure and from that, two routes are possible (Figure 1). One involves the release of vasoactive substances and stimulation of the Autonomic Nervous System (ANS) leading to vascular damage (a vasculitis). The earliest changes are increased lung water, peri-bronchial cuffing, increased airway resistance in terminal bronchioles, earlier airway closure and more shunt. Therefore, of early diagnostic significance is an increased alveolar-arterial oxygen difference. The vasculitis causes alveolar transudates which in turn result in alveolar atelectasis, stiff lungs and venous admixture. The second route possible after blood

vessel closure is that damage to the pneumocyte occurs. This leads to a decreased production of surfactant which in turn produces alveolar atelectasis and the stiff lungs. Probably both mechanisms occur to produce the syndrome.

Blaisdell *et al*⁸ have suggested that tissue trauma, endotoxin release, ischaemia and acidosis will lead to intravascular coagulation (Figure 2). As a result of this, pulmonary thromboemboli are formed. Constrictor substances are released leading to bronchoconstriction and venoconstriction. Microvascular obstruction will lead to alveolar and endothelial cell damage. These events in turn will produce the pathological findings of pulmonary edema and congestion, atelectasis, hyaline membrane formation and intra-alveolar hemorrhage.

FIGURE 2



Robin *et al*¹⁵ have recently demonstrated two cases in which diffuse abnormalities of capillary permeability possibly related to circulating endotoxin produced hypovolaemic shock, generalised edema, hemoconcentration and florid pulmonary edema. Intravenous administration of Dextran 70 (MW 70,000) and Dextran (MW 500,000) led to the accumulation of these compounds in pulmonary edema fluid at a rate consistent with abnormally high pulmonary capillary permeability. The authors conclude that the ARDS results either from increased pulmonary capillary permeability or abnormalities of pulmonary interstitial solute removal.

Understanding certain physiological considerations is critical in the management of the ARDS. Alveolar hyperventilation is common at the outset of the syndrome because of increased respiratory drive and because the wide distribution of intrinsic pulmonary lesions allows hyperventilation of the normal intervening lung tissue. Later, however, hypoventilation may predominate.

Many alveolar units are normally underperfused and the combination of pulmonary congestion and decreased

blood flow may render large numbers of units totally ischemic. The net effect is to increase the volume of alveolar dead space. Increased total ventilation may compensate for this decrease in alveolar volume but in severe shock, this mechanism may further accentuate the tendency toward alveolar hypoventilation.

In the ARDS, striking unequal distribution of $\dot{V}_A/\dot{Q}_c$ ratios, due to continued perfusion of non-ventilated alveolar units produces marked increases in the alveolar arterial oxygen difference and profound decreases in P_{aO_2} . Although the presence of large groups of alveolar units with low $\dot{V}_A/\dot{Q}_c$ ratios is common in C.O.P.D., total alveolar collapse with venoarterial shunting is characteristic of the lung in shock.

Venoarterial shunting is actually a special case of unequal distribution of ventilation and perfusion when the $\dot{V}_A/\dot{Q}_c$ ratio is zero. The level of oxyhaemoglobin saturation of blood leaving a unit with a $\dot{V}_A/\dot{Q}_c$ ratio approaching zero (a totally collapsed unit) is the same as that of mixed blood. Severe shunting produced in the ARDS may constitute up to 50% of the cardiac output and may lead to a profound depression of arterial

oxygen tension. Also a low cardiac output with low venous O_2 tension contributes significantly to further lowering of O_2 tension.

It can be shown that giving oxygen to a patient with a low V/Q ratio will significantly raise the PaO_2 . However, oxygen will have no effect on alveolar units where the V/Q ratio is zero (a totally collapsed unit). Therefore, the aim of therapy is to re-establish the integrity of the alveolar units such that oxygen can be transported across the alveolar membrane.

PRINCIPLES OF MANAGEMENT

This includes support of ventilation and gas exchange and minimizing further pulmonary damage.

1. Prevent alveolar collapse and maintain oxygenation.
 - a. tracheostomy
 - b. volume ventilator
 - c. oxygen control
 - d. positive end-expiratory pressure (PEEP)^{3, 16}
 - e. extra-corporeal oxygenation
2. Prevent further injury
 - a. oxygen control — F_{IO_2} below 60% if at all feasible
 - b. fluid restriction
 - c. antibiotics for specific infections
 - d. corticosteroid drugs.

PEEP is fundamental in improving oxygenation by decreasing the alveolar-arterial oxygen difference. This will allow the use of lower inspired oxygen concentrations in most cases. It is possible that the use of high pressure constant volume, and end-expiratory pressure all provide local tamponade of circulation to areas of good ventilation and these techniques maintain alveolar stability by preventing alveolar collapse on expiration. Areas of non-ventilation are probably not changed. PEEP increases functional residual capacity and reduces right to left shunting. End-expiratory pressures of 5-15 cm H_2O are used and in clinical situations no apparent adverse affect on venous return and cardiac output can be noticed. It is likely that this small back pressure is dissipated across the stiffened lung and is therefore not "felt" by the pulmonary circulation.

Fluid overload can only lead to further difficulties in an already precarious oxygenation situation. The possibility of transudation into alveolar spaces must be kept in mind. Therefore, the judicious use of diuretics is recommended. One must also keep in mind that circulatory support is critical in maintaining cardiac output. This may involve digitalis, β adrenergic drugs and anti-arrhythmia drugs and packed cell transfusions for O_2 content (1 unit of packed cells may be worth 10 mm O_2 tension). Corticosteroid drugs are known to combat the effect of fat found in lungs in the RDS associated with

massive trauma⁴. Corticosteroids have been shown to be effective both clinically and in laboratory models of fat embolism. They may also enhance the secretion of surfactant which is decreased in the ARDS and which is needed to maintain alveolar stability.

In the foreseeable future, the use of membrane oxygenators for short periods of time¹¹ may provide the final step in the therapy of the ARDS. Using extracorporeal oxygenation will buy time for the patients lung to recover on its own when conventional therapy has failed.

ACKNOWLEDGEMENT

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Polyarteritis Nodosa: A Clinicopathological Review

Polyarteritis nodosa with its haphazard involvement of the medium and small arteries of the body can present exceedingly varied clinical pictures while mimicking other diseases. Although its etiology is unknown, hypersensitivity is believed to be the basis for the disease. Experimentally, lesions of hypersensitivity angiitis produced in animals do not always resemble those of polyarteritis nodosa in man¹. An association between the administration and withdrawal of sulphonamides with the onset and remission of polyarteritis has been well documented^{20, 19}. In recent literature, immune complexes related to Australia antigen have been linked to the development of polyarteritis nodosa^{7, 8, 9}. Older studies suggested a prodromal bacterial infection inducing an auto-immune response to the arteries similar to the models for rheumatic fever and post-streptococcal glomerulonephritis^{9, 17}.

The unknown etiology and numerous manifestations of polyarteritis nodosa make the disease difficult to diagnose. Distinction among other arteritides such as Wegener's granuloma, temporal arteritis, systemic lupus erythematosus, rheumatoid arthritis and hypersensitivity angiitis is seldom clear cut, as there may be overlap of symptoms, signs, laboratory tests and histological appearances⁴.

Pathological features are characterized by focal fibrinoid necrosis of the wall of medium and small muscular arteries, usually originating in the media and disrupting the internal elastic lamina. In the acute stage there may be intense neutrophil infiltration associated with fibrinoid necrosis. Healing of the lesion by fibroblastic proliferation and scarring may occur, but often thrombosis or formation of an aneurysm supervenes with resultant infarction of downstream tissue or aneurysmal rupture¹⁵. Glomerulitis of either proliferative or fibrosing nature may occur with or without involvement of the renal arcuate arteries⁴.

The classical clinical presentations are malaise, myalgia, migrating polyarthralgia, weight loss and pyrexia, as shown in 70% of the Mayo Clinic series of 130 cases⁶. Symptoms relating to the urinary tract, gastrointestinal tract, and nervous system are suggestive of polyarteritis nodosa¹⁵. However, when the disease originates in one system and presents a set of local symptoms the diagnosis is difficult and often delayed. Ineffective treatment may account for the poor prognosis. The case at hand is one such example.

CASE HISTORY

The patient, D.M., a 27-year-old white male in previous good health experienced plugging of his left ear in April 1971. This was investigated and diagnosed as serous otitis media. He was treated with decongestants but went on to develop what was considered a purulent

otitis. *Staphylococcus epidermidis*, a common contaminant was cultured. This was treated successfully with ampicillin and decongestants.

Transient vertigo, left ear pain, and plugging recurred in late May 1971. The patient performed a vigorous Valsalva manoeuvre inducing a sudden hearing loss, vertigo and nausea which required hospitalization. A left myringotomy was done and ampicillin was administered. However, the left-sided hearing loss was total. Routine laboratory tests at this time showed hemoglobin, leucocyte count and sedimentation rate to be within normal limits.

In July 1971, similar symptoms were experienced in the right ear and diagnosed again as serous otitis media. In August 1971, he was re-hospitalized. While in hospital he performed another Valsalva to clear his ear. This was associated with sudden hearing loss, vertigo and nausea. Emergency right myringotomy was performed. A right cervical sympathetic blockade was also done presumably to aid in cranial blood flow. Hearing was only slightly improved (15% total) and residual inflammation was treated with low doses of prednisone (15 mg/day). In addition, sulfadimethoxine was given prophylactically for the following 8½ months. Laboratory tests at this admission again revealed a normal hemoglobin, leucocyte count and sedimentation rate. At this time, negative anti-nuclear factor and VDRL tests were noted. Serum electrophoresis showed an elevated beta globulin fraction.

With tapering of the prednisone in February 1972, myalgia, migrating polyarthritides and subcutaneous nodules became evident. In April 1972, ACTH was discontinued, but additional symptoms of left conjunctivitis, hemorrhagic nasal discharge and paraesthesiae in the ulnar distribution of both hands developed.

Severe pain of the joints and muscles necessitated the patient's final admission on 4 May, 1972. Inflammatory swelling of ankles, wrists, and shoulders, and left calf tenderness were confirmed. Other findings were a myopathic facies, pyrexia, grade 2 retinopathy and a pansinusitis. At this stage the patient was normotensive. The clinical impression was that of an arteritis, which was a manifestation of polyarteritis or rheumatoid arthritis, or systemic lupus erythematosus. Urinalysis was reported as normal. Laboratory investigations revealed a low hemoglobin (13 gm%), mild leucocytosis (13,000) with no eosinophilia. The sedimentation rate was 50 mm/hr. Rheumatoid factor was positive (1/640) while anti-nuclear factor and VDRL tests remained negative. Mumps, tuberculin and histoplasmin skin tests were negative while the patient demonstrated immunologic competence with a positive Varidase skin test. Alkaline phosphatase was slightly elevated (14 K.A.) but rose to higher values (24 K.A.) later in the course. Tests for

cryofibrinogen were positive. Serum electrophoresis showed normal globulin levels, lowered albumin and elevated α_1 and α_2 globulins. Repeated blood cultures taken throughout the course of the disease were negative. Immunologic tests for Australia Antigen were negative on two occasions. A muscle and skin nodule biopsy taken early during the patient's hospitalization were non-contributory.

Firm evidence of renal involvement occurred on May 12 with erythrocytes and erythrocyte casts found in the urine. Although microscopic hematuria occurred for the remainder of the patient's illness, renal function remained well with serum creatinine levels never rising above 1 mg%. Open renal and muscle biopsies performed on May 27 revealed a focal and segmental glomerulitis and an acute arteritis with fibrinoid necrosis in the muscle specimen. The patient was initially treated with prednisone 40 mg/day, but this was increased to 80 mg/day over the month of May. A short course of high dosage A.S.A. did not afford significant relief of arthritic symptoms.

The patient deteriorated markedly by June 1972 with progressive fatigue, myalgia and profound pelvic girdle weakness. Electromyographic studies confirmed that he had a severe generalized polyneuropathy with much muscle wasting. For the first time hypertension of 150/110 mm Hg was noted. Azathioprine (IMURAN[®]) treatment (100 mg/day) was initiated on June 5. On June 7, he had episodes of severe colicky epigastric pain accompanied by GI bleeding and absence of bowel sounds. It was suspected that there was polyarteritic involvement of the bowel with possible infarction. A serum amylase taken at this time was within normal limits. Abdominal films were non-contributory. Although muscle symptoms abated somewhat, on June 13, he deteriorated further with extreme weakness rendering him bed-ridden with nausea and a left lateral rectus paralysis. Blood pressure rose to 180/110 mm Hg. Later on the following day he was found to be obtunded. A non-traumatic lumbar puncture demonstrated increased intraspinal pressure and two hundred crenated rbc's/ml. The abdominal right upper quadrant was markedly tender with guarding. A low hemoglobin (10 gm%) and analysis of stomach aspirate indicated some bleeding in the GI tract. The patient was transferred to the Montreal Neurological Institute. On June 15, the patient was unresponsive to pain stimuli. A low sodium level (101 meq/L) and low plasma osmolality (220 mOsm) were discovered upon electrolyte examination. Conversely, there was a high urine osmolality (440 mOsm) and the syndrome of inappropriate A.D.H. secretion was diagnosed. The patient expired several hours after this finding.

AUTOPSY

At autopsy there were typical pathologic manifestations of polyarteritis nodosa. Examination of the GI tract revealed vasculitis selectively affecting the small

and medium sized muscular arteries at the site of mesenteric insertion to the gut. Multiple infarctions of the small bowel were segmental and circumferential, and were clearly related to the arteritis and thrombosis (Fig. 1). About 1.8 metres distal to the ligament of Treitz, a section of infarcted bowel showed a small (0.5 cm) perforation which oozed fecal fluid. Bowel distension was marked and bowel loops were matted with fibrinopurulent exudate. The stomach exhibited diffuse hemorrhages with nodules related to vasculitis. The overlying gastric mucosa showed well delineated plaques and some shallow ulcers. The transverse colon revealed a discrete area of stenosis (1 cm. diameter) related to fibrosis in the wall but with only minimal mucosal abnormality. A more recent lesion was discovered in the descending colon which showed a circumferential mucosal erosion, thickening of the submucosa and muscularis along with serosal fibrosis.

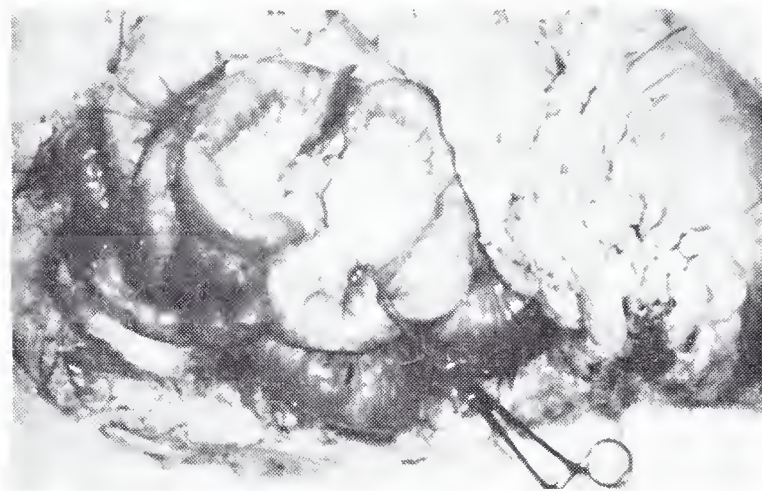


Figure 1: Stomach, small and large bowel with numerous infarcts in the small bowel.

Classical renal involvement by polyarteritis was noted in both kidneys. There were old and fresh ischemic infarctions and many small local hemorrhages (Fig. 2). One muscular arcuate artery showed gross evidence of arteritis and resultant thrombosis. The testicles were seen to be affected by hemorrhagic infarcts.



Figure 2: Wedge shaped hemorrhagic infarct in the renal cortex.

Multiple small arterial thromboses were seen in skeletal muscles and skin. In one specimen the arteritis ap-

peared to involve the vasa nervorum of an adjacent nerve. The adrenal glands showed a marked degree of cortical atrophy related to steroid therapy, and a small area of infarction.

The brain was only mildly swollen. Small subarachnoid hemorrhages were seen over the left parietal and right occipital lobes which when cut showed thrombosis and infarction in the cortex of both areas. The thalamic region appeared grossly normal.

MICROSCOPIC FINDINGS

Acute arteritis with characteristic lesions of fibrinoid necrosis, destruction of the internal elastic lamina, and polymorphonuclear cell infiltration of the vessel wall was found in many tissues. In some vessels, the arteritis had progressed to healing with fibrosis (Figs. 3, 4). The sections of small bowel showed infarction with mucosal necrosis, transmural necrosis and bacterial infiltration. Examination of the transverse colon revealed an old fibrous lesion in the hypertrophic muscle wall related to a healed arteritis. The adrenal glands showed arteritis in the peri-adrenal fat presumably related to a fresh infarct involving a full-thickness segment of cortex. The pancreas showed numerous areas of parenchymal dissolution, fibrosis and necrosis associated with polymorphonuclear cell aggregations. The liver demonstrated fatty infiltration of the hepatocytes, evidence of biliary stasis and the presence of gram negative bacilli. In addition, there was an old fibrosed arteritic lesion found in the portal area. The kidneys were both involved with old and recent infarcts. Acute and healing lesions of arteritis were seen in the arcuate and smaller renal arteries. About 25% of the glomeruli showed either a fibrosing or proliferative glomerulitis with occasional epithelial crescents. Sections of nerve and muscle showed ischemic damage and the usual vascular changes of vasculitis. The brain showed typical involvement of arteritis in the areas of infarction. The thalamic region revealed no specific changes.

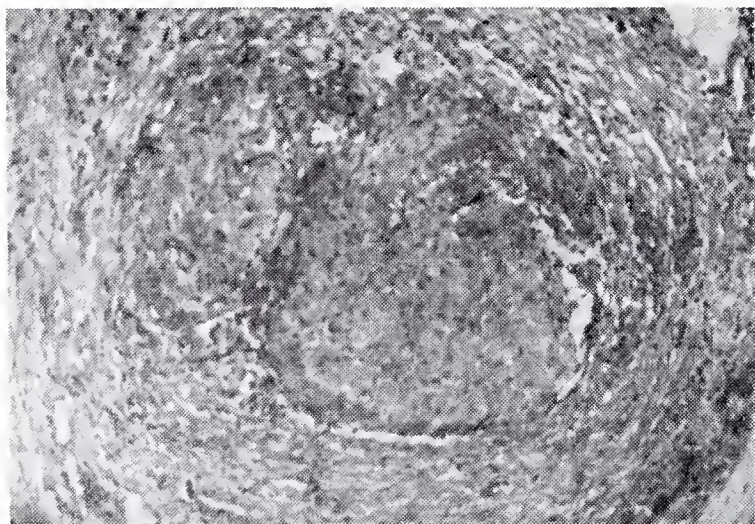


Figure 3: High power H and E stain of small muscular mesenteric artery with peri-arterial inflammation disruption of internal elastic lamina and thrombosis.

The myocardium and coronary arteries showed absolutely no lesions of arteritis or its effects. The lungs also

were notable for the lack of gross and microscopic signs of vasculitis. Some small areas of hemorrhage and clumps of bacteria were all that could be seen.

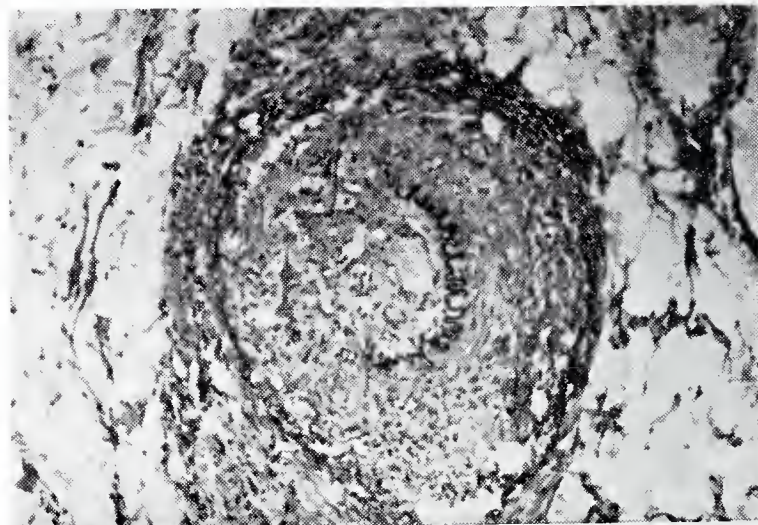


Figure 4: High power elastin stain of small mesenteric artery showing disruption of internal elastic lamina.

SPECIAL STUDIES

Studies using the fluorescent antibody technique on kidney tissue revealed focal areas of glomerular fluorescence of a smooth nature with antifibrin and anti-IgM (Fig. 5). With these two stains there was also fluorescence in and around renal arcuate arteries involved in the arteritic process with a spill-over fluorescence in the peri-arterial tissue (Fig. 6). Anti-bodies specific for the B-1 complement component and Australia antigen showed only a non-specific diffuse fluorescence which was interpreted as a negative result.

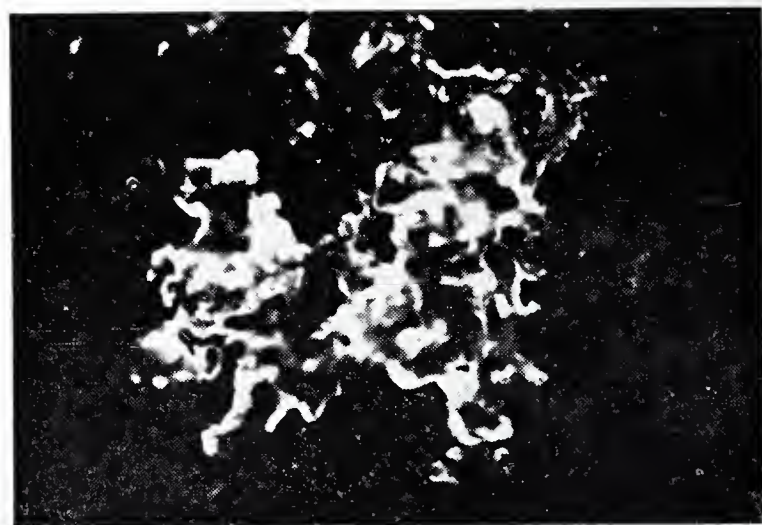


Figure 5: Renal glomerulus with antifibrin fluorescence.

Postmortem bacteriological studies cultured heavy growths of *E. coli* and enterococci in the blood, lungs and peritoneal cavity confirming the initial autopsy impression of sepsis. Peritoneal fungal culture was negative.

COMMENTS

In summary, there was arteritis involving the nervous system, both central and peripheral, the entire gastrointestinal tract with additional involvement of liver and

pancreas. Arteritis involving kidneys and testes completes Robins' criteria for suspicion of polyarteritis¹⁵. Involvement of voluntary muscle and skin was clearly evident. The heart and lungs were apparently spared but this need not be considered an unusual negative finding as clinical involvement of heart and lungs occurs in 10 and 38 percent of cases respectively⁶.

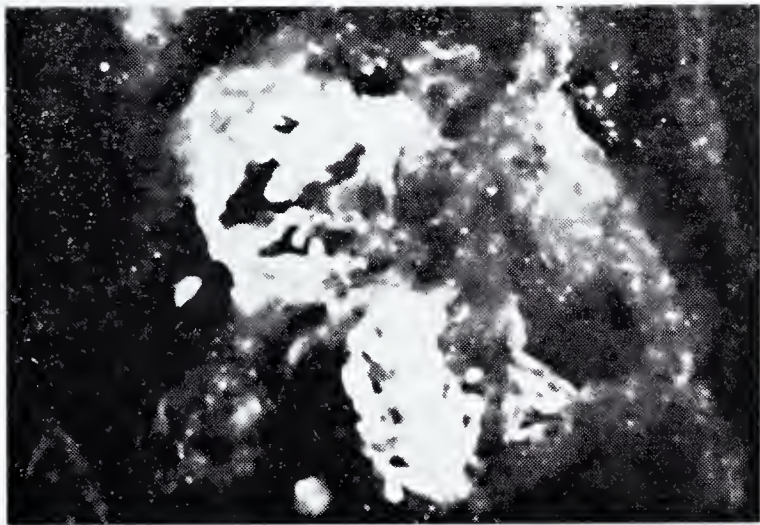


Figure 6: Glomerulus and renal arteriole demonstrating antifibrin fluorescence.

Regrettably, the middle and inner ears were not removed for examination. However, to extrapolate to similar cases, a serous exudate has been demonstrated in the middle ear in conjunction with fibrinous granulation tissue around the foramina rotundum and ovale. In one patient, a one-sided invasion through the foramen rotundum and into the vestibule by granulation tissue was noted with involvement of the semi-circular canals and cochlea. Arteritic lesions were seen below the middle ear mucosa in some cases¹⁴. Several other cases that have presented with ear problems, severe renal disease and granulomatous lung involvement, have been diagnosed as Wegener's granulomatosis with a subheading of polyarteritis^{1, 3, 9}.

The syndrome of inappropriate anti-diuretic hormone secretion (SIADHS) is occasionally present with other forms of cerebro-vascular disease¹⁰. Some form of irritative hypothalamic lesion may have been responsible after the cortical infarctions and increased intra-cranial pressure.

The relationship of the administration of sulfonamides to the onset of polyarteritis in this case is unsatisfactory as, retrospectively, the disease may have antedated the drug administration. There was no flare up of symptoms as was seen in one case report, and there was no apparent clinical improvement upon removal of the sulfonamide⁹.

The effect of steroids on the course of the disease is difficult to assess. The patient became symptomatic on withdrawal of the low dosage prednisone given to alleviate the sensorineural ear symptoms. This appears to be quite common in cases of polyarteritis nodosae. 50% of patients in the Mayo Clinic series, prior to arrival at

the clinic, were put on steroids to relieve symptoms of an undiagnosed or wrongly diagnosed disease⁶. The re-introduction of prednisone failed to arrest the progression of symptoms. However, it has been remarked that treatment with cortisone, although it results in healing of arterial lesion, still permits fibrous obliteration of the arterial lumen with continuation of symptomatology^{3, 2}. It has been well established that there is a significant difference in survival between steroid treated and non-treated patients^{6, 12}. These papers also point out how important it is prognostically to initiate appropriate therapy early and before hypertension or severe renal disease supervenes.

Azathioprine (Imuran^(R)) therapy begun in June was probably given too late. Lorenzen pointed out in his series that in advanced stages of disease, therapy failed to prevent progression¹¹. It has also been noted that azathioprine in conjunction with prednisone has produced dramatic remission of symptoms. The relief of myalgia and arthralgia after the initiation of azathioprine may possibly be attributable to the drug¹³. Because azathioprine is a cytostatic drug which influences the humoral and cell-mediated immunological reactions, it and prednisone were probably instrumental in the development of the overwhelming sepsis — one of the hazards of therapy with these agents¹¹.

In conclusion, it must be re-emphasized that polyarteritis nodosa should be recognized early and therapy should be adequate and prompt.

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The neutrophilic granulocytic system is characteristic of one with fine controls. In response to a pyogenic infection it releases enormous numbers of neutrophils into the blood and replaces them by increasing cell production. When infection is under control the production and blood concentration returns to normal. After neutropenia and bone marrow hypoplasia from drug toxicity or irradiation the system can revert to normal. In the absence of such stresses both granulocyte production and delivery to the blood are regulated so that the marrow granulocyte cellularity and blood neutrophil concentration can remain within narrow limits. Both the responsiveness to stress and stability when not under stress demonstrate a system with fine controls¹

In this discussion I will first elaborate a model of myelopoiesis. Hopefully, it will serve as a framework to explain a potential control mechanism of granulopoiesis (CSA) and its possible role in disease states.

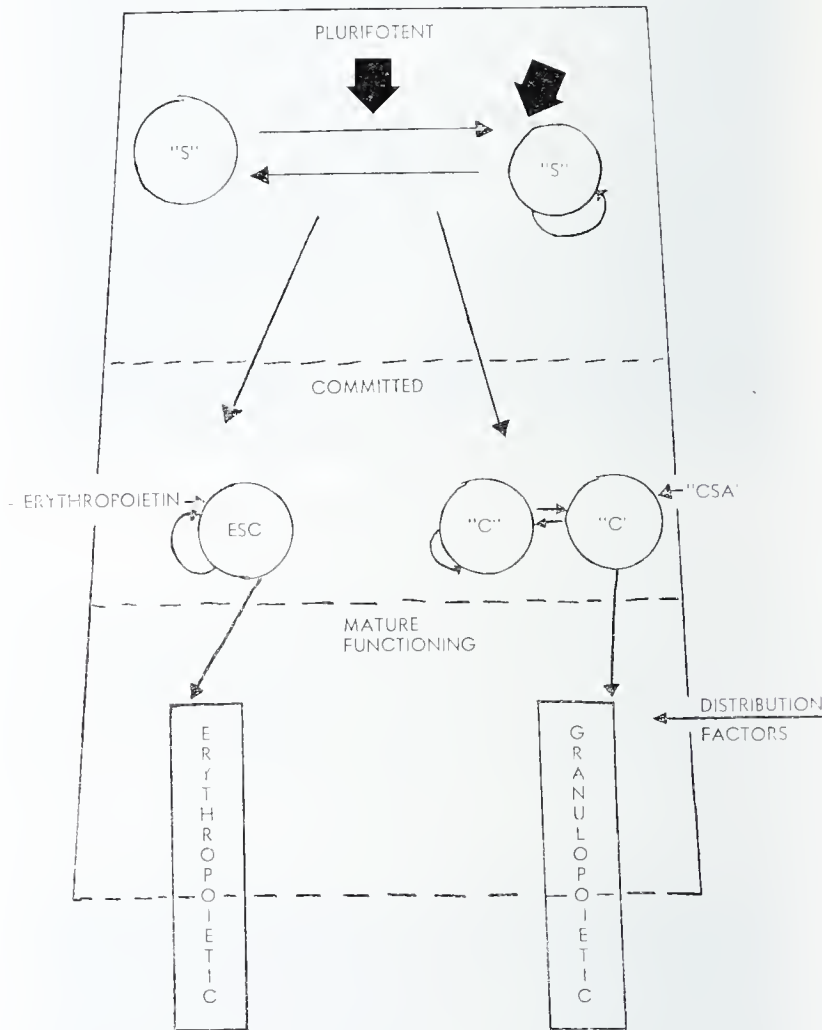
The model I have used is Dr. E. A. McCulloch’s conceptualization². The outline of the figure represents the limit of the haemopoietic organ. Its expanding margins are symbolic of the exponential expansion that occurs during proliferation and differentiation. At the top of the diagram pluripotent stem cells are in two physiologic states: the majority are at *rest* but able to undergo a reversible transition with a population of proliferating cells. Self renewal is symbolized by an arrow. The margins of the haemopoietic organ surrounding pluripotent cells is shown to be *solid* indicating that this compartment is relatively isolated from regulatory influence occurring elsewhere in the body. Control is achieved by *short term regulators*, shown as arrows and acting either to affect the partition of cells between resting and cycling states or upon self-renewing compartment.

Pluripotent stem cells are not morphologically recognizable. They are capable of *irreversible* transitions to committed progenitors of erythropoiesis or granulopoiesis which are also not morphologically recognized. The latter labelled C(CFU-C) is so named for their capacity for colony forming in culture. Indirect evidence is available that committed precursors of erythropoiesis exist; such cells are responsive to the hormone erythropoietin and are designated ESC (erythropoietin sensitive cells). The margins surrounding the committed compartment are open; regulators derived from other parts of the animal enter this compartment to affect CFU-C and ESC. For erythropoiesis, the regulator is erythropoietin whose primary site of production is the kidney. For granulopoiesis, colony stimulating activity (CSA) is shown in a position analogous to that of erythropoietin. While CSA is required *in vitro* for colony formation its physiologic role is still conjectural.

The last compartment contains the maturing, *morphologically* recognizable erythropoietic and granulopoietic cells. This contains everything from the myeloblast to the promyelocyte, myelocyte, metamyelocyte to the band

and polymorph. This compartment is shown closely related to the peripheral blood; *mature* forms are outside the hemopoietic organ and at least for the polymorphonuclear leukocytes, regulatory mechanisms exist that influence the anatomic distribution of functional cells.

Figure 1: A Minimal Model of Myelopoiesis²



The different control mechanisms acting at three levels in myelopoiesis have survival value. Pluripotent stem cells are essential for continuing hemopoietic function. They require protection from external influences that might lead to their depletion and hence they respond to *local* influences regulating population size. Committed progenitors form the basis for independent regulation of separate cell lineages derived from a common progenitor; therefore, these need to respond to external influences bearing information from other organ systems.

Both long- and short-range regulators acting on *progenitors* have numerically greater effects on the delivery of functional cells because of the amplification inherent in exponential growth. These effects are delayed by the time needed for proliferation and differentiation. Accordingly there exists a final regulator called “leukocytosis inducing factor”. This humoral factor is capable of mobilizing granulocyte reserves from the marrow to meet *immediately* the requirements imposed by bacterial invasion or trauma. It does not appear to directly stimulate granulopoiesis.

So far I have tried to provide a basic structure of hemopoiesis showing the present state of knowledge. I will now turn specifically to the granulopoietic part and in particular to CSA.

Colony formation *in culture* from cells of normal human marrow or peripheral blood has two basic requirements: a viscid suspensory material (agar or methyl cellulose) and colony stimulating activity (CSA). CSA is a cell product either elaborated in culture or obtained from body fluids. Partial purification has been achieved and the activity has been tentatively identified with a glycoprotein of molecular weight 45,000-190,000. (Note: erythropoietin is also a glycoprotein). For human cells the most reliable source of CSA is peripheral leukocytes. Supernatants of these cells have been found to be active. Human cells in culture will form small colonies even without addition of CSA. Such colonies are small and it is probable that their development depends on small amounts of CSA produced by cells added to the assay. Messner has recently shown that human marrow appears to contain both granulopoietin progenitors and a cellular source of CSA.

Demonstration that normal sera from some species of mice will stimulate colony formation and recent evidence that perturbation of the granulocytic compartment may generate increasing amounts of CSA has raised the inevitable question as to whether CSA is a granulopoietin analogous in its action to erythropoietin.

Where is CSA produced? Some people feel that the mature granulocyte contains a regulator of granulopoiesis. Some support for this idea is provided by the observation that induction of neutropenia with anti-neutrophil serum is associated with increasing amounts of CSA. However, if the death of the granulocyte was associated with release of a stimulator for further differentiation this unlike most other biologic control systems would be a positive feedback. Thus, ever increasing granulopoiesis would result in the face of a granulolytic response, but would fail to provide a stimulus in neutropenic states (eg. established infection)⁴.

CSA activity is generated after endotoxin treatment in animals with pre-existing neutropenia, even in animals where neutrophil count approaches zero. This would appear incompatible with the notion that CSA is produced by the mature granulocyte. The monocyte, which presumably is present in the peripheral blood buffy coat layers used in the culture of human marrow, may be the source of CSA. However, it seems likely that there is either one widely distributed cell responsible for production eg. the monocyte or macrophage, or one tissue which is common to many organs, eg. connective or vascular tissue. Such widely distributed cells or tissues would permit a granulocytic response to local infection. This might account for the reports that CSA can be extracted from such diverse tissues as spleen, kidney, pregnant uterus and salivary gland.

The relationship of CSA to endotoxin is interesting.

Within minutes of injection of endotoxin into mice an increase in CSA may be observed. In irradiated animals increased levels of CSA are seen at a time which corresponds to the time of onset of bacteremia and septicemia. The latter may result from radiation damage to the intestinal mucosa and entrance of bacteria from the intestinal flora into the systemic circulation. Their further growth is favoured by decreased phagocytic activity as a result of radiation induced neutropenia. Of potential interest is the fact that *germ free* animals when irradiated do not develop the increase in CSA which is seen in conventional irradiated animals. This could account for the presence of CSA in various organ extracts and after diverse perturbations. The day-to-day regulation of myelopoiesis may be accounted for by intermittent bacteremia and endotoxemia alone or perhaps in association with normal tissue breakdown⁵.

I would now like to briefly show how CSA may be involved in disease states in man: namely leukemia. McCulloch and Till showed that colony formation is abnormal in untreated leukemia. In acute myeloblastic leukemia (AML) colony formation is reduced. A reduction has also been observed in patients with pre-leukemias many months prior to the development of the overt disease, indicating that the change in colony formation efficiency may be closely related to the disease. Remission-induction in AML is regularly associated with striking increases in marrow colony-forming efficiency. However, early in remission, colony formation is markedly dependent on exogenous CSA even when marrow cells are plated at high density. As remission induction proceeds, dependence of colony formation on exogenous CSA decreases perhaps indicating a return toward normal in CSA producing cells. If this hypothesis can be confirmed experimentally it will support the view that an interaction between CFU-C and CSA producing cells is part of the mechanism of hemopoietic regulation *in vivo*³.

It has been my goal to demonstrate how CSA may fit into the broad spectrum of hemopoiesis. Evidence so far suggests but as yet does *not prove* that CSA is a physiologic stimulator of granulopoiesis. However, experiments to confirm its role are now taking place. The answers arrived at may soon place it as an important regulator of granulopoiesis thus enabling us to better understand white cell replication and to control it in disease states.

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The Investigation of a Case of Combined Hypothalamo-Pituitary Insufficiency

Victor Likwornik

The developments of assays for measurement in the serum of LH, FSH and TSH along with the availability of TRH and LH/FSH-RH have been utilized in clinical tests which yield information permitting better understanding of the disorders in the hypothalamic-pituitary-target organ axis.

The following case history illustrates the ways in which the above mentioned tests were used in the investigation of a patient with multiple endocrine abnormalities.

Mr. T. E., a 31-year-old white male presented at the St. Bartholomew's Hospital on 23/11/72 complaining of polydipsia, double vision, weight gain, and loss of sex function.

About two and a half years earlier, he had started having episodes of double vision which appeared only when the patient was tired. Then, in January, 1972, he noticed some blind spots in his visual field. In March he started having early morning headaches which passed away during the day. A few weeks later his memory became very poor and his headaches became worse. He began vomiting three days prior to his admission to Queen Square on April 4, 1972.

On admission he was found to have a fluctuating level of consciousness from minute to minute. When drowsy, he was unable to lift his eyes above the horizontal; but had no nystagmus. At best, he was disoriented with respect to time and place, and was unable to do simple arithmetic. He had early papilloedema greater on the left than on the right side, as well as right homonymous hemianopia, failure of upward gaze, and failure of convergence.

In his upper limbs he had drift of outstretched R. hand, cogwheel rigidity at wrist on the right greater than on the left and loss of fine movement in both hands. Abdominal reflexes were present. In the lower limbs he had a right upgoing plantar and a left downgoing plantar; the position and vibration senses were impaired in the right but not in the left foot. Down the right side of his body there was an inattention deficit. There was no dysphagia.

The EEG and brain scan both suggested a deep left hemisphere lesion. Left carotid arteriogram showed abnormal circulation in the same region, suggestive of a malignant glioma.

All the laboratory findings with respect to the E.S.R., W.B.C., electrolytes, R.B.C., uric acid and liver and renal function, were normal.

The patient was treated with 10 mgs Dexamethasone O.D. and within 24 hours made such a dramatic re-

covery that a biopsy was not felt to be justified at that time, because the risk outweighed the therapeutic gain.

In August, 1972 he was readmitted for review: L. carotid arteriogram was repeated and found to be normal with no signs of the previous pathological circulation; there was only slight R. sided hyperreflexia and some left eye muscles weakness. The patient now appeared Cushingoid and it was decided to reduce his steroid dose to 0.5 mg. Dexamethasone daily, by October, 1972. At about this time he started complaining of severe thirst and polyuria, drinking 11 pints of water per day.

He was readmitted to St. Bartholomew's on November 11, 1972 for investigation of his endocrine status.

On functional enquiry it was noted that he had gained 4 kgs in the past 10 months, had some nausea and constipation (one bowel movement every 4 days with difficulty), and was suffering from polydipsia and polyuria (20 pints of water per day D/N - 8/3). Vision, and mild paraesthesiae in the right hand.

On physical examination he was found to be an obese man with a buffalo hump and small testes. The reflexes on his right side were increased moderately, and he also had diplopia which was found to be due to a complete fourth and partial third nerve paralysis of his left eye. The fundi were normal. His B.P. was 110/80.

His Hb, WBC, electrolytes and liver function tests were all within the normal limits. C.S.F.: protein 66 mg%, sugar 47 mg%, W.R. negative.

His P.B.I. was 2.5 μ g% (normal 4-8 μ g%); T_3 resin uptake was 121% (normal 97-122). The chest and skull x-rays were normal.

EVALUATION OF ENDOCRINE STATUS

POSTERIOR PITUITARY

The patient was passing 10 litres of urine per 24 hours; his plasma osmolality was 290 mOsm/kg, and urine osmolality was 90 mOsm/kg. In order to administer the Water Deprivation Test to diagnose diabetes insipidus the patient was first made euthyroid, and put on correct steroid replacement. After only 5 hours of water deprivation he had lost 3.5% of his body weight and the test was terminated. The urine osmolality throughout the test remained at 90 mOsm/kg; his plasma osmolality went up from 285 to 300 mOsm/kg, and there was no detectable ADH in his urine. Administration of 20 μ g of DDAVP (desamino dextra arginine vasopressin) increased his urine osmolality to 700-800 mOsm/kg.

It was concluded that the patient had vasopressin

deficient diabetes insipidus due to a hypothalamic lesion.
ANTERIOR PITUITARY

LH-FSH: random LH was less than 0.4 mU/ml, and this remained unchanged after 10 days of Chlomiphene administration (normal LH levels run in excess of 2.0 mU/ml, and rise in response to Chlomiphene). After administration of LHRH as described in the "LHRH stimulation test" at the end of the article, the patient's LH levels again failed to rise above 0.4 mU/ml.

His 17-ketosteroids were 4.4 mg/day (normal 5 - 20 mg/day); his 17-hydroxy-androgens were 1.7 ng/ml (normal male levels are 5 - 22 ng/ml).

Therefore, he was gonadotrophin deficient. This could be due to either pituitary damage or due to a combined hypothalamic-pituitary lesion.

TSH

His PBI was 2.5 μ g% (normal 4 - 8 μ g%); T_3 resin uptake was 121%, (normal 97-122). The results of the "TRH stimulation test", performed as described at the end of the article, were:

Time (mins.)	TSH μ U/ml
0	0.4
20	1.4
60	2.1

This pattern of response is suggestive of chronic lack of TRH due to a hypothalamic lesion. Therefore, he was hypothyroid probably due to a TRH deficiency due to hypothalamic damage.

Hypothalamic-pituitary-adrenal axis:

He was admitted on 5 mg. Prednisone b.i.d., and the 0900 hrs. plasma cortisol was 5.5 μ g%. After receiving 2 mg depot Synacthan (= ACTH) on the second day his plasma cortisol was 28 μ g% and after three days it was 39 μ g%. Several days later 0.1 mg Synacthan was administered I.M. and in 15 mins. the plasma cortisol level rose to 33.5 μ g%, and at 30 mins. rose to 41.5 μ g%. Having established the ability of the adrenals to respond to ACTH, the patient was now given the Insulin Tolerance Test. This required the administration of 0.2U insulin/kg. wt. The blood sugar level fell to 30 mg% but the plasma cortisol did not rise above 6.5 μ g% (normal rise is above 21 μ g%).

The adrenals had good reserve capacity, but poor response to stress; this is suggestive of ACTH deficiency.

The patient was also given i.v. LVP (lysine vasopressin) infusion of 4 units over 2 hours. This, in healthy people, liberates ACTH from the pituitary by direct action on it. In this case there was no rise in plasma cortisol, indicating inadequate pituitary function with respect to ACTH.

During the Insulin Tolerance Test there was no rise

of G.H. above 5 ng% (in normals it rises to 20 ng% or more). Therefore, either the pituitary or the hypothalamus or both were impaired.

From the above mentioned investigations it was concluded that the lesion involved certain parts of both the hypothalamus and the pituitary.

Sarcoidosis of the hypothalamic-pituitary area was thought to be the most likely underlying disease process.

The patient was discharged on:

DDAVP (desamino dextra arginine vasopressin)
— 10 μ g b.i.d. nasal spray

Thyroxine 200 μ g/day

Prednisone 7.5 mg/day

Sustenon (testosterone propionate) 250 μ g I.M. two times per week.

HORMONAL RESPONSES TO SYNTHETIC L.H.R.H. - F.S.R.H. IN MAN¹

LH/FSH-RH is a decapeptide, and on I.V. injection causes an increase in serum immunoreactive LH with a peak at 20 to 30 mins.; increase in immunoreactive FSH is also noted. Similar results are obtained with two different immunoreactive assays. LH/FSH-RH therefore causes both LH and FSH release in man but does not affect GH, TSH, or ACTH. LH and FSH responses are the same in men as in women; however, in men the serum levels of gonadal steroids are not changed significantly. In women there was a rise in oestradiol after 100 μ g dose of LH/FSH-RH.

Use of LH/FSH-RH will be important to define the level of the lesion in hypogonadal patients and in the treatment of some types of male infertility. A patient who shows no gonadotrophin response to Chlomiphene but an adequate response to LH/FSH-RH would be expected to have a lesion above the pituitary, but an absent response to the releasing hormone would indicate pituitary disease. If Chlomiphene and LH/FSH-RH responses are present the defect would be in the gonads. This would also elucidate whether so called isolated gonadotrophin deficiencies are indeed deficiencies of hypothalamic releasing factors rather than of pituitary production.

The test consists of administration of 100 μ g LH/FSH-RH I.V. and blood samples for LH and FSH before and 20 and 60 mins. after administration.

TSH RESPONSE TO SYNTHETIC TRH IN MAN²

The increase in serum TSH levels measured 20 and 60 mins. after I.V. injection of 200 μ g of synthetic TRH (thyrotrophin-releasing hormone) has been used as a test of pituitary-hypothalamic function. Of 15 patients with various hypothalamic lesions 13 had a delayed response to TRH, where the 20 min. TSH level was less

than the 60 min. value. This delayed pattern of response can be used to recognize hypothalamic disease.

TRH releases preformed TSH from the pituitary into circulation and also increases TSH synthesis. The magnitude of the change in serum TSH levels 20 mins. after TRH administration probably reflects the reserve pituitary TSH content and this may be reduced owing to loss of thyrotroph cells in patients with pituitary disease.

In patients with hypothalamic disease reduced pituitary TSH content is the result of a prolonged lack of TRH stimulation of the TSH producing cells. The delayed rise in serum TSH levels observed in majority of patients with hypothalamic disease may be a consequence of the time required for TRH to initiate synthesis of TSH. Therefore, a delayed pattern of response is an indirect indication of hypothalamic disease.

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